International Journal of Rheumatic Diseases

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Journal:	*International Journal of Rheumatic Diseases*
Manuscript ID:	IJRD-2015-0030.R2
Manuscript Type:	Original Article
Date Submitted by the Author:	n/a
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Keywords:	Rheumatoid arthritis, Clinical aspects < Rheumatoid arthritis, Disease aetiology and pathogenesis – human < Rheumatoid arthritis

Increased disease activity, severity and autoantibody positivity in rheumatoid arthritis patients with co-existent bronchiectasis.

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Running head: Bronchiectasis and rheumatoid arthritis severity

Key words: Anti-CCP, bronchiectasis, disease activity, rheumatoid arthritis, rheumatoid factor,

ABSTRACT

Aim: Patients with rheumatoid arthritis (RA) and co-existent Bronchiectasis (BRRA) have a 5-fold increased mortality compared to rheumatoid arthritis alone. Yet previous studies have found no difference in clinical and serological markers of RA disease severity between BRRA patients and RA alone. RA disease activity measures such as DAS28-CRP and anti-cyclic citrullinated peptide antibodies (anti-CCP) however have not been studied, so we assessed these parameters in patients with BRRA and RA alone.

Methods: BRRA patients (n = 53) had HRCT proven bronchiectasis without any interstitial lung disease and ≥2 respiratory infections/year. RA alone patients (n = 50) had no clinical or radiological evidence of lung disease. DAS28-CRP, rheumatoid factor (IgM) and anti-CCP were measured in all patients, together with detailed clinical and radiology records.

Results: In BRRA, BR predated RA in 58% of patients. BRRA patients had higher DAS28 scores (3.51 vs. 2.59), higher levels of anti-CCP (89 vs. 46%) and RF (79 vs. 52%) (p = 0.003) compared to RA alone. Where hand and foot radiology findings were recorded, 29/37 BRRA (78%) and 13/30 (43%) RA alone had evidence of erosive change (p = 0.003). There were no significant differences between groups in smoking history or DMARD/biologic therapy.

Conclusions: Increased levels of RA disease activity, severity and RA autoantibodies are demonstrated in patients with RA and co-existent bronchiectasis compared to patients with RA alone, despite lower tobacco exposure. This study demonstrates that BRRA is a more severe systemic disease than RA alone.

INTRODUCTION

The association between Rheumatoid arthritis (RA) and bronchiectasis (BR) has been recognized for many years. Indeed, in 1967 Walker observed an ten-fold increased prevalence of bronchiectasis in an RA population when compared to a population of patients with degenerative joint disease [1]. Modern studies have found symptomatic bronchiectasis with a prevalence of 2.7% in RA subjects, compared to 0.03% in the general population [2]. High resolution computed tomography (HRCT) studies demonstrate the prevalence to be much higher, with radiological BR in RA populations repeatedly reported in the region of 30% [3-6].

Studies have addressed the characteristics of RA patients with bronchiectasis with no consensus in terms of presence or absence of a positive rheumatoid factor, rheumatoid nodules, joint damage and functional impairment [5, 7, 8]. Infectious complications in patients with RA and bronchiectasis are common and have serious implications for management with disease modifying anti rheumatic drug (DMARD) and biologic therapy [9]. Despite this, two small contrasting studies have evaluated DMARD and biologic therapies in patients with RA and co-existent BR. One study demonstrated lower infective exacerbations of BR in patients on DMARDs [10], while the other found more infective exacerbations in patients on biologics [11]. The co-existence of these conditions has significant health implications, indeed patients with RA and BR have been shown to have mortality rates 7.3 times that of the general population, 5 times that of patients with RA alone and 2.4 times that of patients with BR alone [12].

The temporal relationship and significance of the association between BR and RA has been a subject of great interest for many years. Numerous studies have found that BR precedes RA often by 20-30 years [1, 8, 13, 14], supporting the hypothesis that BR may be involved in the pathogenesis of RA [1, 8, 13, 14]. In contrast, other studies have demonstrated RA precedes BR and argue that BR is an extra-articular manifestation of severe late RA [9, 15]. Importantly, recent HRCT studies demonstrate an increased prevalence of subclinical airway abnormalities consistent with BR at first diagnosis in RA patients [16, 17] supporting the hypothesis that BR typically precedes RA and that BR could play a role in the pathogenesis of RA.

Previous studies of BR and coexistent RA are limited in terms of disease definition, indeed the majority pre-date HRCT and modern tests for RA autoantibodies, particularly anti-CCP antibodies. Previous studies of patients with HRCT proven BR and co-existent RA have been limited by low numbers, with typically less than 25 cases reported [8, 13, 18, 19]. Initially no link between anti-CCP and lung disease was found [20], but two studies have reported an association between anti-CCP and airways disease [21] and interstitial lung disease [22] in patients with established RA. Recently, Demoruelle and co-workers [16] have identified an association between anti-CCP positive subjects without inflammatory arthritis and the presence of airway abnormalities on HRCT. This evidence supports the hypothesis that the lung may be an initiating site for the development of RA.

This cross-sectional observational study details the natural history, disease severity and RA autoantibody positivity in the largest study of well-defined HRCT proven non-cystic fibrosis BR and co-existent RA subjects reported to date [17-19, 23]. We have compared the results with those obtained from a control group of RA patients with no evidence of lung disease.

SUBJECTS AND METHODS

Subjects were chiefly identified by review of RA and BR patient databases searching for those with documented co-existent disease in respective specialist clinics at four different hospitals across the UK. These comprised Freeman Hospital, Newcastle upon Tyne; Queen Elizabeth Hospital, Gateshead; Royal Cornwall Hospital, Truro and North Bristol NHS Trust Hospital. Rheumatology and respiratory consultants at participating hospitals were contacted directly and invited to participate by confirming their willingness to allow access to their patients with twin diagnoses of RA and BR, together with access to their medical records. To address any potential sources of recruitment bias, site of recruitment and method of identification was recorded for each participant allowing study outcome measures to be compared between these sub-groups. Ethical approval was obtained at all centres participating in this study (multi centre ethics – IRAS 12324) and conforms to the provisions of the Declaration of Helsinki in 1995. All recruitment was completed between May 2012 and May 2013.

We identified adult patients (>18 years) with HRCT proven symptomatic non-cystic fibrosis BR reported by an independent radiologist and a history of ≥2 respiratory infections per year determined by a clinician who met the 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) criteria for RA [17-19, 23]. Patients with any other form of lung disease in addition to BR were specifically excluded from the study. This included all those with established interstitial lung disease, asthma or advanced emphysema. All participating centres employed these criteria. In this current study we did not assess the severity of bronchiectasis by HRCT, but we would consider doing so in future more detailed studies. All BRRA patients were under specialist respiratory follow-up, their annual pulmonary function tests and the number of lower respiratory infections requiring antibiotics in the past 12 months were recorded as part of the study.

In addition to patients with BR and co-existent RA we recruited 50 control RA patients. These patients met the ACR/EULAR criteria [24] for RA but had no clinical or radiological evidence of any lung disease. They were consecutively identified from the same hospital sites, using the same mechanisms over the same time period. Moreover, All RA control patients were reviewed by a physician and had a normal clinical examination, with no evidence of respiratory symptoms. Chest x-ray and lung function

results were also reviewed for all RA patients and when they were performed, were within normal limits.

Data collection

We recorded demographic details, together with the date of onset of symptoms and date of diagnosis for RA and BR by face-to-face assessment undertaken by one of us (EP). Current RA therapy and a detailed smoking history were also recorded. RA disease activity and severity measures were recorded for both groups including the disease activity score in 28 joints (DAS-28) performed by a single Rheumatologist (EP), C-reactive protein (CRP) levels, radiological evidence of erosive disease and RA autoantibody status. RA Remission was defined by a DAS28-CRP score <2.6 [25].

Anti-CCP was measured in serum by ELISA assay using the Phadia Elia ^{TM} CCP (2nd generation). We classified levels of <7 U/ml as negative, levels of 7-10 U/ml as equivocal and levels >10 U/ml as positive. In accordance with ACR classification, positive results were subdivided with results greater than 30 U/ml (three-fold the laboratory upper limit of normal) considered high positive. Levels above 340 U/ml (the upper detection limit) were considered very high positive. Measurement of rheumatoid factor (RF) in participant serum was performed using ROCHE Diagnostics Hitachi Modular P. We classified levels <14 U/ml as negative and levels >14 U/ml as positive. Once more, positive results were subdivided using a definition of >3 times the upper limit of normal to define highly positive and measures above the upper detection limit >130 U/ml to define very highly positive.

Receiver operating characteristics (ROC) curves were generated comparing test results for RF and anti-CCP between RA patients versus BRRA patients, using Prism 5 software and the area under each ROC curve calculated, together with 95% confidence intervals.

Statistical analysis

Continuous variables are expressed as median +/- interquartile range (IQR). Fisher's exact test, the Mann Whitney U test and multivariate analysis were used to compare categorical variables and outcome measurements between the two groups of patients with RA and BR and the Kruskal-Wallis test to compare variables between greater than two groups. Comparisons of diagnostic specificity and sensitivity were

made together with positive predictive values (PPV) and negative predictive values (NPV) for patients in both cohorts, positive for either RF, anti-CCP or both. All statistical tests were two sided and P values <0.05 were considered statistically significant.

RESULTS

BR and RA Natural History: We identified 53 patients with non-cystic fibrosis BR and coexistent RA (BRRA). Among these, in 31 cases (58%) symptoms of BR preceded the onset of RA by a median (IQR) of 25 (19) years. In another 21 (40%), RA symptoms preceded BR by a median (IQR) of 18 (14) years. In the remaining individual, BR and RA symptoms developed simultaneously. The delay between symptom onset and diagnosis differed significantly for the two conditions. While 43 (81%) reported that the onset of RA symptoms occurred within 12 months of the diagnosis of RA, only 21 (40%) reported that the diagnosis of BR was made within a year of the onset of respiratory symptoms (p<000.1). Indeed, the median duration of delay between BR symptom onset and diagnosis for the 53 cases identified was 11.87 years in comparison to 2 years for RA. All BRRA patients had HRCT evidence of Bronchiectasis without any other lung disease. Although fibrotic lung disease is a recognised complication of disease modifying therapy serial HRCT scans were beyond the scope of this study. It is therefore impossible to exclude new drug induced pathology, however all BRRA patients were under specialist respiratory follow-up and were excluded from the study if evidence of fibrotic lung disease was found on HRCT or in their clinical history.

Demographics: In addition to the 53 BRRA patients we recruited 50 RA controls without lung disease. The gender and age distribution was similar between the two groups, however patients with BRRA were found to have a longer duration of RA (Table 1). To control for this we frequency matched 38 RA patients as case controls for 38 BRRA patients by RA disease duration (Table 2).

RA Disease Severity and Activity: Comparison of BRRA and RA alone patients demonstrate a clearly statistically significant increase in DAS28-CRP in BRRA patients of almost 1.0 unit, p=0.003 (Table 1). These differences remained when the groups were matched for RA disease duration (Table 2). In addition all components of the DAS28-CRP disease activity score except VAS (global) were significantly

higher in the BRRA group compared to the RA group matched for RA duration (Figure 1).

Where hand and foot radiology findings were recorded a significantly higher percentage of BRRA patients had evidence of erosive disease, once more this increase remained when the groups were matched for RA disease duration (Table 1, 2). Remission rates defined by a DAS28-CRP <2.6 [25] were considerably lower for the complete BRRA group compared to the RA group [9% versus 28% (p = 0.0001)] and for the BRRA group matched for RA disease duration [6% vs 19% (p = 0.002)] (Table 1, 2).

Smoking History: There was no significant difference in the proportion of ex/current smokers for the complete BRRA group compared to the RA group [22% versus 28% (p = 0.1)] or the BRRA group matched for disease duration [16% versus 18% (p = 0.8)]. Low mean number of pack years in the ex-smokers was observed in both groups (Table 1, 2). Therefore there was no need for statistical adjustment based on smoking as a confounder.

Serology: In total 47 (89%) of the BRRA patients were anti-CCP positive, compared to 46% for RA alone (Table 3). The sensitivity (89% versus 79%) and NPV (82% versus 69%) for RABR was higher for anti-CCP than RF. This is in agreement with previous studies. Notably the proportion of BRRA patients with very highly positive anti-CCP results was far greater than the RA group [49% versus 18% (p = 0.001)] (Figure 2B). Similarly, the proportion of BRRA patients with very high positive titres for RF was significantly statistically different from those with RA alone [32% versus 14% (p = 0.037)] (Figure 2A). There was a high level of concordance between RF and anti-CCP. Indeed, of the anti-CCP positive BRRA patients, 42 (89%) were also positive for RF. For the RA group 23 (46%) were anti-CCP positive, the level of concordance with RF was similar to the BRRA group with 21 (91%) also positive for RF. The combination of measuring RF and anti-CCP antibodies gave a moderate increase in the specificity of 58% compared with measuring only RF (48%) or anti-CCP (54%) alone. The presence of bronchiectasis constituted a greater risk factor for developing both anti-CCP and RF antibodies. The values for specificity, sensitivity and both positive and negative predictive values are shown in Table 3.

ROC analysis provided further evidence that both the RF and anti-CCP assays discriminates between BRRA and RA group of patients. The area under the curve for anti-CCP was 0.7302 (P < 0.0001; 95% CI 0.63 – 0.83) and for RF 0.7087 (P < 0.0003; 95% CI 0.61 – 0.81) (Fig 2 C and D). This indicated that patients with BBRA had higher test results for anti-CCP and RF than RA patients, 73% and 71% occasions respectively; suggesting anti-CCP has a higher diagnostic performance than RF for distinguishing between BRRA and RA alone. If no difference between the two groups existed, a value of 0.5 would have been expected. The ROC curve for anti-CCP passed closer to upper left hand corner than the RF ROC curve indicating that the sensitivity compared at the same specificity value, was higher for anti-CCP antibody titres than RF antibodies (Figure 2C & D).

RA Therapeutics: There was no significant difference in the proportion of patients on no DMARD or biologic therapy, DMARD monotherapy, DMARD combination therapy or biologic therapy between the complete BRRA group and the RA group or the BRRA group and the RA group matched for disease duration (Table 1, 2) and were not considered confounders warranting statistical adjustment. However both the complete BRRA group (10/53) and the matched BRRA group (7/38) had a significantly higher proportion of patients on oral prednisolone compared to both the unmatched RA groups (1/50) and matched RA groups (1/38) (Table 1, 2). In previous studies intra-articular steroid injection in RA patients can result in diminished ESR and CRP levels [26]. However in our study CRP levels in BBRA versus RA patients was consistently higher, despite a higher number of BBRA patients being treated with oral prednisolone compared to RA patients.

Effect of different Recruitments sites/methods: There were no significant differences in mean values of DAS28-CRP in those RA patients with BR identified by local clinicians as opposed to those identified by database [mean 3.65 versus 3.38 (p=0.28)]. Furthermore, there was no difference between DAS28-CRP scores between the 4 recruitment hospital sites [median Bristol 2.88 versus Freeman 3.45 versus Gateshead 3.1 vs Cornwall 3.7 (p = 0.12 Kruskal-Wallis test)].

DISCUSSION

All measures of disease activity and severity were found to be significantly higher in the BRRA group compared to the RA alone group. This difference remained when the groups were matched for RA disease duration. Despite these findings DMARD/biologic treatment was no more aggressive in the BRRA group suggesting under treatment of RA in this patient group. It is likely this reflects common clinical concerns that DMARD/biologic treatment may exacerbate respiratory infections [9, 11]. The challenge faced by clinicians is highlighted by the significant increase in prednisolone use in the BRRA group. Prednisolone is often prescribed when there are concerns over infection risk despite itself being well recognised to increase the risk of infections [27, 28]. Indeed, there is currently no consensus on DMARD/biologic therapies in patients with RA and co-existent BR and further studies are urgently required, especially given the prevalence rates of up to 30% [3-6].

While we have analysed the sensitivity and specificity of anti-CCP and RF to determine the co-existence of BRRA, It would be misleading to give a specific cut-off value for the level of anti-CCP or RF to predict the co-existence of BR and RA from this study. Indeed, it is important to recognise that given RA autoantibody positivity was lower in our RA alone group than would be expected in the general RA population, if this low level is a chance result it would result in a gross over-estimate of the sensitivity of anti-CCP and RF to determine the presence of BR. To determine a cut off value with any certainty larger numbers would be required, including patients with RA alone with HRCT evidence confirming the absence of lung disease. This was not possible within the restrictions of our ethics.

Based on ROC curve analysis, we demonstrated that the presence of anti-CCP antibodies and RF in BRRA patients had a better diagnostic performance than in RA alone. RA autoantibodies levels, especially anti-CCP, were very strongly positive in the BRRA group significantly more so than among RA controls. However, tobacco consumption (a well-recognised environmental risk factor for anti-CCP positive RA [29]) was low, suggesting that other factors must drive the very high levels of anti-CCP positivity. The very high levels of anti-CCP antibodies in our BRRA group, in addition to recent findings of high levels of antibodies to citrullinated peptides in bronchiolar lavage fluid [30], subclinical HRCT lung abnormalities at diagnosis of RA [17] and

increased prevalence of lung abnormalities in RA-autoantibody positive subject without RA [16] all support the hypothesis that lung pathology may play a role in the development of anti-citrulline immunity in the pathogenesis of RA [30, 31]. In our previous study, we found that bronchiectasis patients with no evidence of RA had higher RF positivity compared to age-sex matched controls. A small but significant proportion of these were also anti-CCP positive and over a 12 month period developed RA [32] .

RA-autoantibody level positivity and the proportion of patients on biologic therapy were lower than anticipated in our RA alone group for UK clinical practice despite identical recruitment methods. This may reflect our exclusion of RA patients with any clinical or radiological evidence of lung disease. This is the correct control group in the context of this study. Indeed, if the hypothesis that lung pathology plays a role in the development of anti-citrulline immunity in RA is correct, we would expect to see lower RA autoantibodies, lower disease activity and lower RA severity in a selected group of RA patients without evidence of lung disease compare to an unselected RA patient group.

Limitations of our study include the possibility of unrecognised case selection bias. In addition, we did not introduce any formal mechanism for double-checking the results of CT scanning reports.

In summary we have demonstrated high levels of RA disease activity, severity and RA autoantibodies in a group of patients with RA and co-existent bronchiectasis in spite of little tobacco exposure. Further research involving patients with RA and co-existent bronchiectasis is required on a pathogenesis level to investigate the potential role for lung pathology in the development of citrulline immunity in RA and on a clinical level to help guide physicians in selecting appropriate therapeutic options for this challenging patient group.

ACKNOWLEDGEMENTS

We acknowledge funding support from Arthritis Research UK to EP (Grant 19894) and a Higher Education Funding Council for England (HEFCE) senior lectureship to ADS. PE and DH wish to acknowledge support by Cornwall Arthritis Trust, Northcott

Devon Medical Foundation, and the Dutchy Health Charity. We also acknowledge National Institute for Health Research CLRN support to the recruiting centres via the UK Comprehensive Research Network portfolio:

(http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=12324). None of these authors have any conflicts of interest to declare.

Figure legends

Figure 1: Individual (**A**) joint scores and (**B**) CRP/VAS components of DAS28-CRP for patients with RA alone (RA) with RA co-existent bronchiectasis (BRRA). Groups matched for RA disease duration (BRRA n=38, RA n=38). Differences between groups was assessed using the Mann-Whitney Test; * $p<0.05$; ** $P<0.01$; ns – not significant

Figure 2: Comparative frequency and degree of seropositivity for (**A**) RF and (**B**) anti-CCP in BRRA (n=53) and RA (n=50) alone. ROC curves for the measurement of (**C**) rheumatoid factor and (**D**) anti-CCP in BBRA vs. RA patients. Area under the curves for RF is 0.7087, for anti-CCP 0.7302

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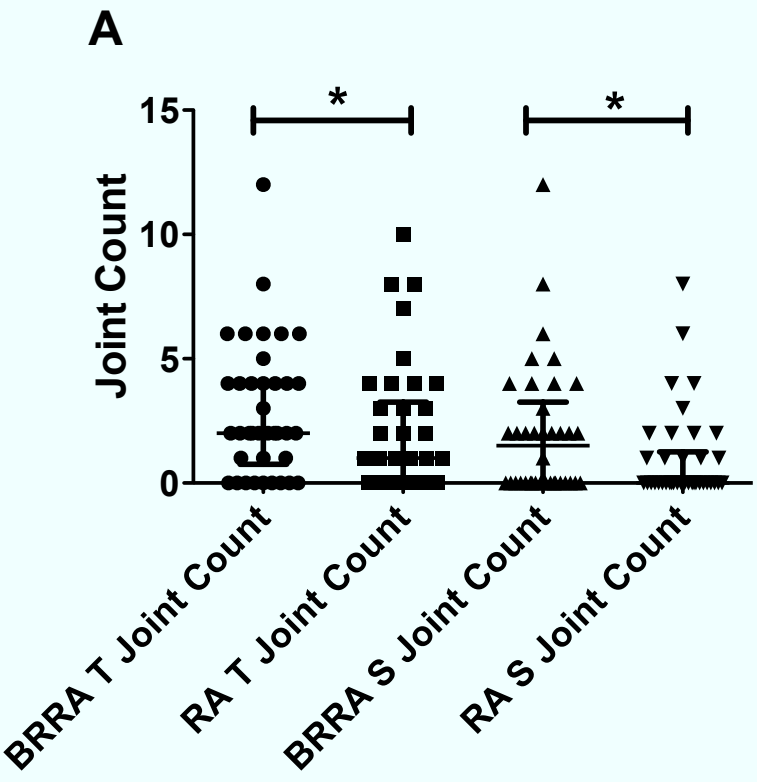
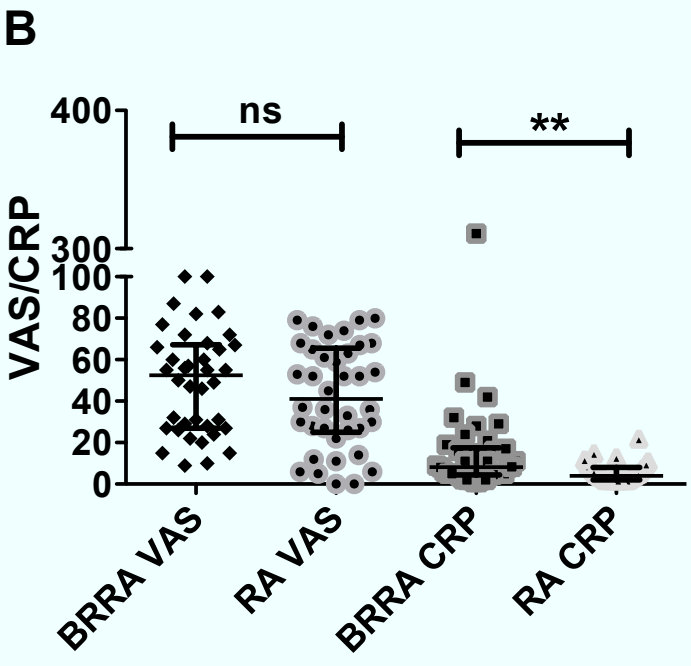
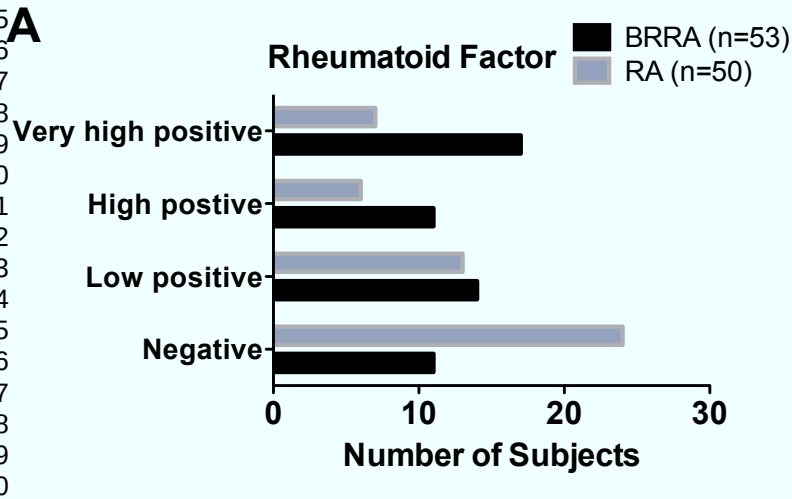
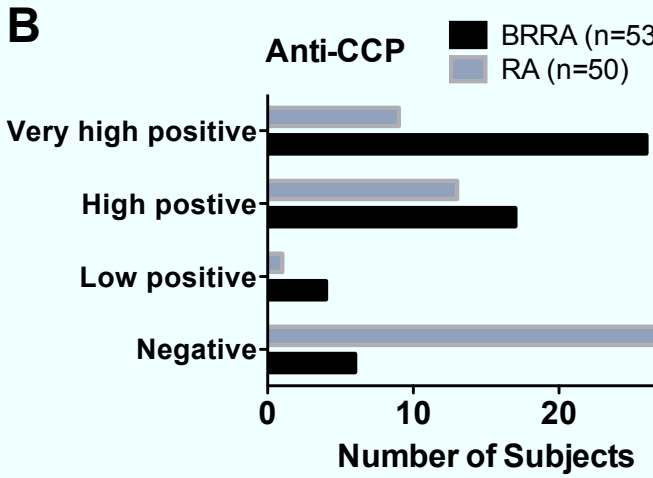


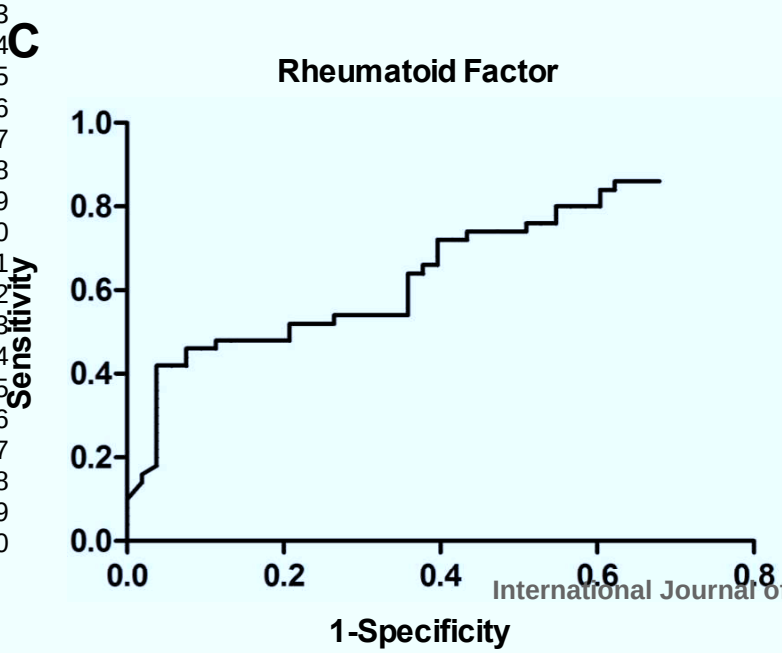
Median (IQR)
BRRA T Joint Count = 2 (3.25)
RA T Joint Count = 1 (3.25)
BRRA S Joint count = 1.5 (3.25)
RA S Joint Count = 0 (1.25)



Median (IQR)
BRRA VAS = 53 (40)
RA VAS = 41 (41)
BRRA CRP = 8.2 (13.1)
RA CRP = 4.1(6.0)







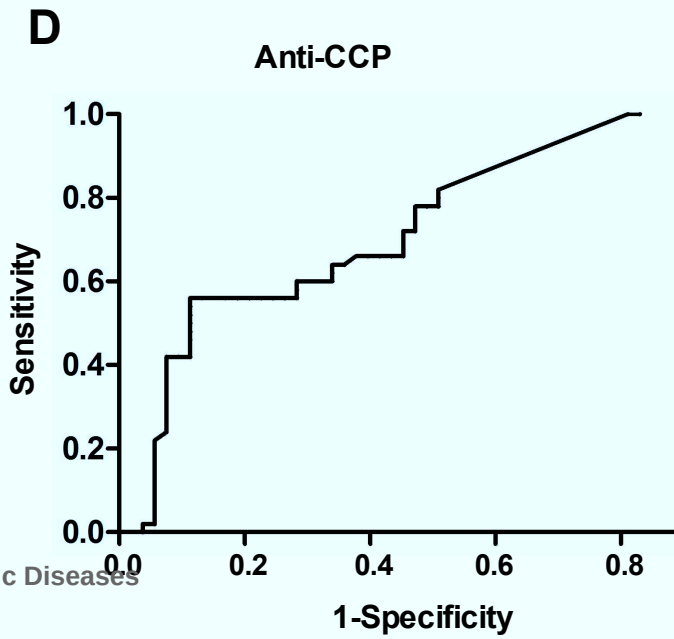


Table 1: Characteristics of patients with RA with and without co-existent Bronchiectasis

Demographics	BRRA (n=53)	RA Alone (n=50)	p value
Female, number (%)	38 (72)	36 (72)	1.000
Age in years, median (IQR)	69 (12)	66 (15)	0.069
Duration RA in years, median (IQR)	19 (24)	12 (14)	0.001*
Smoking History			
Ex/Current Smoker, number (%)	22 (42)	28 (56)	0.101
Pack Years, median (IQR)	0 (12)	3 (20)	0.232
Disease Activity/Severity			
DAS28-CRP, median (IQR)	3.51 (1.16)	2.59 (1.76)	0.003*
Erosive Disease on X-ray, number (%)[i]	29 (78)	13 (43)	0.003*
RA in remission, number (%)[ii]	9 (17)	28 (53)	<0.0001*
RA Autoantibody Positivity			
ACPA positivity, number (%)	47 (89)	23 (46)	<0.0001*
RF positivity, number (%)	42 (79)	26 (52)	0.003*
RA Therapeutics			
No current DMARD/Biologic therapy, number (%)	7 (13)	3 (6)	0.32
DMARD monotherapy, number (%)	25 (47)	27 (51)	0.56
DMARD combination, number (%)	12 (23)	17 (34)	0.27
Biologic, number (%)	9 (17)	3 (6)	0.13
Oral prednisolone, number (%)[iii]	10 (19)	1 (2)	0.0082*

i. Limited x-ray data available, n= 37 BRRA and n=30 RA alone.
ii. RA Remission defined by a DAS28-CRP score <2.6 [26]
iii. Oral prednisolone either alone or in combination with DMARDs/Biologics

Table 2: Characteristics of patients with RA with and without co-existent Bronchiectasis matched for RA disease duration

Demographics	**BRRA** (n=38)	**RA Alone** (n=38)	**p value**
Female, number (%)	27 (71)	27 (71)	1.000
Age in years, median (IQR)	70 (12)	66 (13)	0.100
Duration RA in years, median (IQR)	13 (13)	12 (12)	0.871
Smoking History			
Ex/Current Smoker, number (%)	16 (42)	18 (47)	0.818
Pack Years, median (IQR)	0 (17)	0 (19)	0.841
Disease Activity/Severity			
DAS28-CRP, median (IQR)	3.45 (1.13)	2.59 (1.84)	0.006*
Erosive Disease on X-ray, number (%)[i]	20 (74)	8 (36)	0.009*
RA in remission, number (%)[ii]	6 (16)	19 (50)	0.002*
RA Autoantibody Positivity			
ACPA positivity, number (%)	32 (84)	17 (45)	0.001*
RF positivity, number (%)	28 (74)	19 (50)	0.058
RA Therapeutics			
No current DMARD/Biologic therapy, number (%)	5 (13)	2 (5)	0.430
DMARD monotherapy, number (%)	17 (45)	19 (50)	0.819
DMARD combination, number (%)	8 (21)	14 (37)	0.206
Biologic, number (%)	8 (21)	3 (8)	0.191
Oral prednisolone[iii]	7 (18)	1 (3)	0.029*

i. Limited x-ray data available, n= 27 BRRA and n= 22 RA alone.
ii. RA Remission defined by a DAS28-CRP score <2.6 [26]

Table 3: Diagnostic performance of rheumatoid factor (RF) and anti-CCP in patients with RA with and without co-existing lung disease (LD)

Serology	RA	RA+LD	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
RF+ve*	**68/103 (66%)**	**42/53 (79%)**	**79 (0.66-0.89)**	**48 (0.34-0.63)**	**62**	**69**
RF+ve* [8]	48/64 (75%)	24/32 (75%)	75 (0.57-0.89)	25 (0.11-0.43)	50	50
RF+ve* [24]	49/63 (78%)	16/21 (76%)	76 (0.53-0.92)	21 (0.10-0.37)	33	64
RF+ve** [22]	182/252 (72%)	48/59 (81%)	81 (0.69-0.90)	31 (0.24-0.38)	26	84
Anti-CCP+ve*	**70/103 (68%)**	**47/53 (89%)**	**89 (0.77-0.96)**	**54 (0.39-0.68)**	**67**	**82**
Anti-CCP +ve** [22]	223/252 (88%)	57/59 (97%)	97 (0.88-0.99)	14 (0.09-0.20)	26	93
RF & anti-CCP+ve*	**63/103**	**42/53**	**79 (0.66-0.89)**	**58 (0.43 - 0.72)**	**67**	**73**

* RA vs. RA and coexisting bronchiectasis; **RA vs. RA and coexisting lung disease. Bold depicts data from current study.